Specialty Conference

Photochemical Air Pollution Part II

Moderator
ELLIOT GOLDSTEIN, MD

Discussants
DONALD DUNGWORTH, DVM, PhD; ELLIOT GOLDSTEIN, MD, *and* PAOLO F. RICCI, PhD

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DONALD DUNGWORTH, DVM, PhD:* The heightened contemporary interest in the toxicity of photochemical oxidants has led to many investigations with animals. These studies, in which animals are experimentally exposed to precisely measured concentrations of ozone or nitrogen dioxide (NO_2) alone, in combination or as part of a mixture of pollutants, have provided important information on the consequences of short-term or prolonged exposure to these agents. This discussion focuses on morphologic delineation of the damage caused by photochemical oxidants.

Morphologic Effects of Photochemical Oxidants on Lungs of Experimental Animals

Short-term Effects of Ozone

Depending on the ozone concentration, the short-term (less than 24-hour) pulmonary effects of exposure to ozone range from mild centroacinar inflammation at concentrations of 0.1 to 0.2 ppm[1-4] to death from pulmonary edema at concentrations above 4.0 ppm; the precise lethal concentration varies with species and duration of exposure.[5,6] Because the highest one-hour ozone concentration measured in Los Angeles between 1958 and 1977 was 0.65 ppm,[7] this discussion is limited to morphologic effects produced by ozone at concentrations of less than 1.0 ppm. Also, because ultraviolet absorption photometry is now accepted as the standard for calibrating ozone-measuring instruments, literature values based on potassium iodide calibration curves have been reduced by 80% to provide equivalent ultraviolet photometric concentrations.[8]

The most severe effect of ozone in all animal species that have been studied occurs in the centroacinar region of the lung forming the junctions between airways and alveoli.[9-14] At ozone concentrations of 0.1 to 0.2 ppm, damage is limited to this region.[2,3] Because the structure of the centroacinar region varies with species, differences occur in the exact site of the lesion. In rats, which do not have respiratory bronchioles, the lesion is in the terminal bronchioles and proximal alveolar ducts.[10,12,13] In monkeys, the lesion mainly affects the proximal orders of respiratory bronchioles.[3,14] Because the degree of development of respiratory bronchioles in monkeys more nearly resembles that in humans,[15] this is most likely the site of principal damage in human lungs. Another feature more readily appreciated in monkeys than in rodents is that the trachea and proximal bronchi are more affected than the distal bronchi, though less so than the respiratory bronchioles. This observation is in agreement with mathematical models of airway transportation and uptake of ozone.[16]

The early centroacinar response to ozone has been well characterized in rats[13,17,18] and in monkeys.[15] In rats, alveolar type I cells in proximal alveoli are most sensitive to damage. These cells become necrotic and slough within six hours after exposure to 0.4 ppm of ozone. The denuded alveolar basement membranes are covered by spreading and proliferating alveolar type II cells, which are highly resistant to damage from ozone. Ciliated cells are also sensitive, losing their cilia by two hours after exposure to 0.14 ppm of ozone. Nonciliated secretory bronchiolar (Clara) cells are less affected and, in fact, proliferate to compensate for the loss of ciliated cells by serving as their progenitors.[17,19] Inflammatory cells, mostly macrophages, appear in the lumen of affected bronchioles and alveolar ducts by six hours after

*Professor and Chairperson, Department of Pathology, University of California, Davis, School of Veterinary Medicine.

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Reprint requests to Elliot Goldstein, MD, Chief, Division of Infectious and Immunologic Diseases, Department of Internal Medicine, UCD Professional Bldg, 4301 X Street, Sacramento, CA 95817.

ABBREVIATIONS USED IN TEXT

EPA = Environmental Protection Agency
FEV_1 = forced expiratory volume in 1 second
NO_2 = nitrogen dioxide

the start of an ozone exposure of 0.4 to 0.7 ppm and increase in number through 48 hours when exposure is continued.[13] The early replacement of ozone-sensitive alveolar type I epithelial cells and ciliated bronchiolar cells by alveolar type II and Clara cells is referred to as the "reparative adaptive" period[13] and is a basic pulmonary response to injury. In rhesus monkeys, an analogous sequence of events occurs in the respiratory bronchioles; the net effect is that after 50 hours of exposure to 0.64 ppm of ozone, hyperplastic and hypertrophic bronchiolar epithelium and many adherent alveolar macrophages and polymorphonuclear leukocytes are present.[4] Lesions in major airways are less dramatic than those in centroacinar regions, and damage to ciliated cells is the main change in monkeys[3,14] and in rats.[1] Thus, short-term exposure to ambient levels of ozone is clearly capable of causing morphologic abnormalities in rats and monkeys and, therefore, similar injury is likely in humans.

Intermediate to Long-term Effects of Ozone

Exposure of rats, guinea pigs and hamsters to approximately 1.3 ppm of ozone, 6 hours a day, 5 days a week over a period of 14 months produces lungs with chronic centroacinar pneumonitis and emphysema.[20,21] Exposure of rats to more relevant levels of ozone (0.16, 0.4 or 0.64 ppm, 8 hours a day, for as long as 90 days) provokes centroacinar inflammation, the intensity of which diminishes as the duration of exposure is prolonged.[22] This decrease in intensity is indicated by a reduction in the number of intraluminal mac-

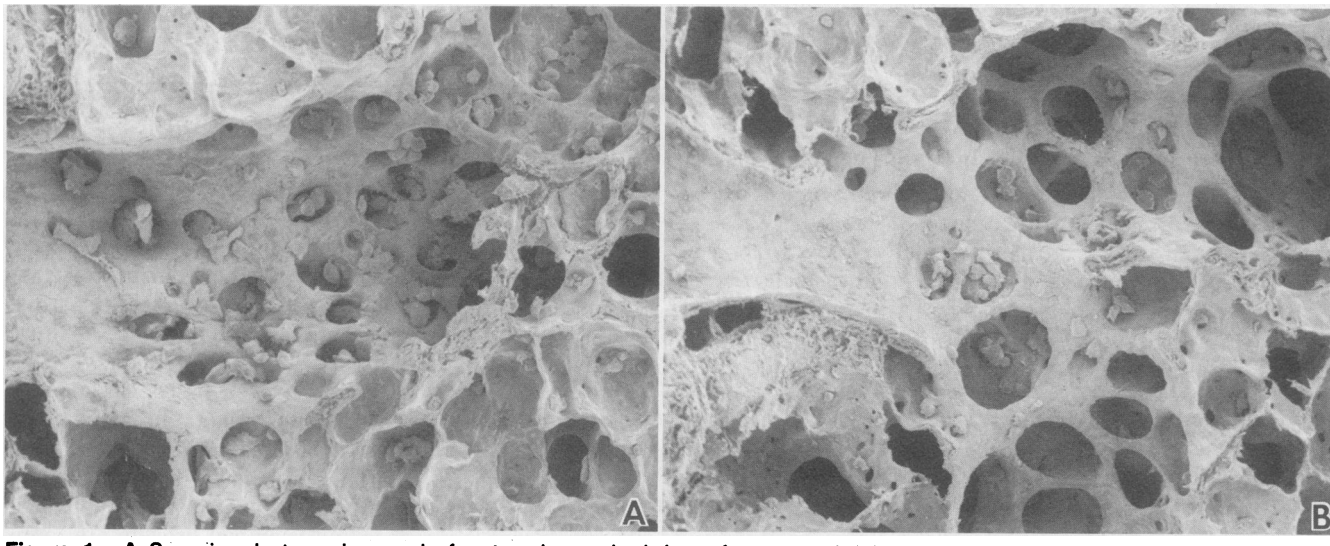

Figure 1.—A, Scanning electron micrograph of centroacinar region in lung of rat exposed eight hours a day for seven days to 0.64 ppm of ozone. Abundant alveolar macrophages accumulate in the region of the rudimentary respiratory bronchiole. **B,** A similar region in a rat exposed to 0.64 ppm ozone for 90 days. The number of macrophages is reduced compared with that of a seven-day exposure, but the alveolar ducts have undergone remodeling. Field width, 250 microns.

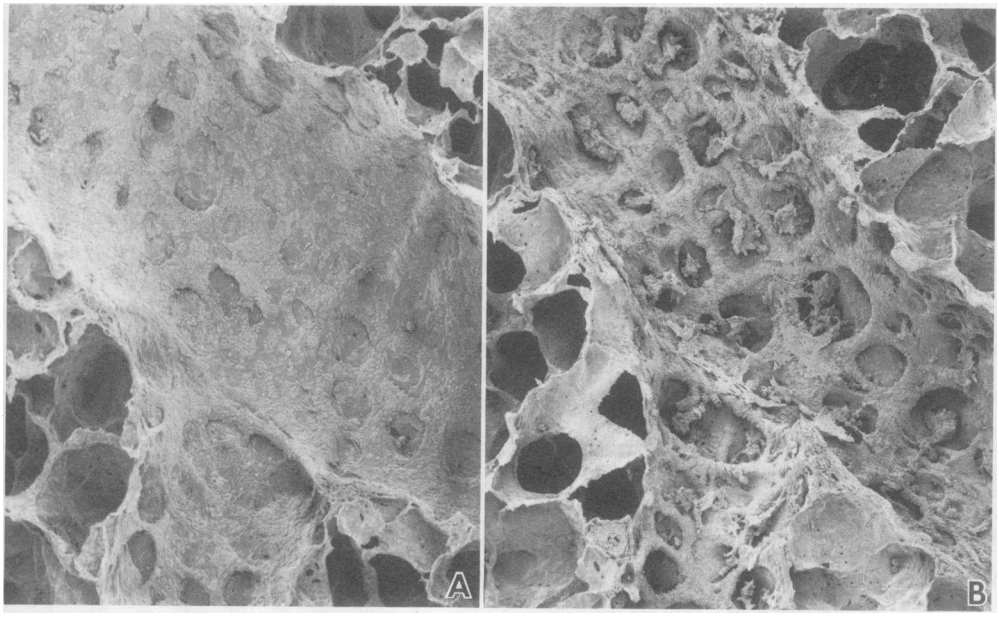

Figure 2.—A, A scanning electron micrograph of normal respiratory bronchiole of a bonnet monkey. The bronchiolar wall is lined by clusters of cuboidal cells interspersed among type I pneumonocytes. **B,** Bronchiolitis caused by exposure of bonnet monkeys to 0.64 ppm ozone 8 hours a day for 90 days. Aggregated inflammatory cells are prominent in alveolar openings and there is hyperplasia of cuboidal bronchiolar epithelium. Field width, 450 microns.

rophages and in the thickness of the blood-air barrier of proximal alveoli. After daily exposures to 0.16 ppm of ozone for 90 days, pulmonary morphology is essentially the same as in controls. At 0.64 ppm, the lesion persists but with less evidence of inflammation and epithelial damage than was present during the first 7 to 20 days of exposure. An additional abnormality of importance is the permanent remodeling of a portion of the centroacinar region to a respiratory bronchiole (Figure 1). Similar changes are found in lungs of rats exposed continuously to 0.4 ppm of ozone for 180 days.[23] Thus, prolonged exposures to ozone result in inflammation and interstitial fibrosis in centroacinar regions and some increase in total lung volume. Even though total lung volume is increased, however, the pathologic changes cannot be classified as emphysema.

Daily exposure of bonnet monkeys *(Macaca radiata)* for 8 hours to 0.4 or 0.64 ppm of ozone for 90 days also results in diminished bronchiolar inflammation at the later times.[24] The hypertrophy and hyperplasia of the bronchiolar epithelium are maintained, but the amount of fibrosis is minimal (Figure 2). After one year of exposure to 0.64 ppm of ozone for eight hours a day, the lungs of bonnet monkeys show a chronic bronchiolitis that is only slightly more severe than that noted at 90 days; they also show a greater number of inflammatory cells and narrower bronchiolar lumens.[25] These more severe abnormalities account for the small but significant increases in airway resistance and the corresponding decreases in forced expiratory volume in one second (FEV_1) observed after one year of exposure.[26]

Effects of Nitrogen Dioxide

Experiments with a wide variety of animals indicate that exposure to very high levels of NO_2 is required to produce death.[27,28] In mice, rats or guinea pigs, the threshold level of mortality following a one-hour exposure to nitrogen dioxide is 40 to 50 ppm.[27] Rabbits and dogs are more resistant,[27] as are monkeys, which survive exposures of eight hours to 65 ppm of NO_2.[28] Brief exposures to high concentrations of NO_2 are much more toxic than equivalent exposure to low concentrations of the pollutant for prolonged periods.

Lesions occur primarily within the lung in animals exposed for less than 24 hours to high levels of NO_2.[27] All species have varying degrees of vascular congestion, edema, bronchiolitis and parenchymal inflammation.[28-31] Short-term exposure to nearly ambient concentrations of NO_2 (2 to 3 ppm) does not result in serious canine or murine morphologic abnormalities.[31,32] At these concentrations, ultrastructural and scanning electromicroscopic studies show losses of cilia, swelling and disruption of type I alveolar cells, fibrin deposition along basement membranes and influxes of macrophages.[31,32] These lesions are transient, and if the insult is discontinued, the damaged tissue is repaired. These and similar results indicate that exposure to nearly ambient concentrations of NO_2 does not provoke pulmonary lesions of the type induced by ambient concentrations of ozone. In fact, it is generally stated that short-term exposure to NO_2 is 1/10th to 1/20th as toxic as to ozone.[33-35]

All animal species studied survive continuous exposure of a year or more to levels of NO_2 of at least 0.5 ppm.[36-41] Mice survive exposure to 0.5 ppm for 12 months,[36] rats survive 0.8 and 2.0 ppm for a lifetime,[37,38] dogs survive 5.0 ppm for 15 months,[39] squirrel monkeys *(Saimiri sciureus)* survive 1.0 ppm for 16 months[40] and stump-tailed monkeys *(Macaca arctoides)* survive 2.0 ppm for 2 years.[41]

Prolonged exposure to ambient concentrations of NO_2 does not appear to cause significant morphologic damage. The lungs of mice, the species most susceptible to nitrogen dioxide-induced injury, show changes consisting of shortening of cilia, edema and proliferation of alveolar epithelial cells following one-month exposure to 0.5 ppm of NO_2.[42] The lungs of rats exposed for their entire lifetime to 0.8 or 2.0 ppm of NO_2 show only ciliary loss, epithelial hypertrophy and "cytoplasmic blebbing."[37,38] Similarly, the lungs of stump-tailed monkeys exposed for 14 months to 2.0 ppm of NO_2 show only hypertrophy of bronchiolar epithelium.[43] Evidence that NO_2 might not be as innocuous as these reports indicate, however, is the finding of mild but functionally detectable emphysema in the lungs of beagles exposed 16 hours a day for 68 months to a combination of 0.63 ppm NO_2 and 0.25 ppm nitrogen oxide with morphologic evaluation after an additional three years in clean air.[44] When animals are exposed long term to much higher concentrations of NO_2 (8.0 ppm and higher), destructive changes in alveolar walls and abnormal enlargements of distal air spaces occur, which resemble emphysematous lesions in humans.[45-47] Because of the high concentrations used in these experiments, the results cannot be extrapolated to NO_2 exposures in humans.

Morphologic Aspects of Adaptation

The term adaptation refers to several different aspects of ozone-induced effects: reduction of airway irritability responses in human volunteers exposed sequentially, protection of experimental animals against death from acute pulmonary edema and alteration of the time course of centroacinar inflammation in experimental animals. Anatomically, the long-term effects of ambient levels of ozone are limited to the centroacinar regions in animals and there is reason to expect that this is the case in humans. Adaptation of importance relative to the risk of long-term effects in humans must be analyzed in terms of cellular changes in this highly vulnerable centroacinar region. Evidence has been presented that the intensity of centroacinar inflammation diminishes during daily exposures to 0.64 ppm of ozone in rats over a period of 180 days[22,23] and in bonnet monkeys over a year.[24,25] At lower levels (0.16 ppm) of ozone, inflammation almost disappears. Thus, adaptation is a transient response to persistent injury, and maintenance of the adaptive state requires continuous or frequently repeated exposure to ozone.[48] Although the pathophysiology of the adaptive state in which sensitive cell types are replaced by resistant ones is unknown, the effect is protective in that the rate of cumulative damage is less than it would be without adaptive changes. Thus, adaptive changes reduce the intensity of bronchiolitis, thereby diminishing the extent of permanent injury produced by a smoldering lesion.

In summary, extensive morphologic investigations have been carried out in animals of short-term and long-term exposures to ozone and nitrogen dioxide. These studies have shown that short-term exposure to ambient concentrations of ozone produces cellular changes and subtle structural abnormalities in pulmonary centroacinar regions of rodents and nonhuman primates; prolonged continuous exposures for up to one year to peak ambient levels affect the same regions,

producing mild bronchiolitis and interstitial fibrosis. Because these lesions are associated with only small physiologic disturbances in nonhuman primates, uncertainty exists regarding the importance of the lesions detected at lower levels of exposure. Ascertaining the importance of these oxidant-induced lesions is an area for future investigation. Similar studies of animals exposed to ambient levels of NO_2 do not show morphologic abnormalities, regardless of the length of exposure.

Effect of Photochemical Oxidants on Susceptibility of Animals to Pulmonary Bacterial Infection

ELLIOT GOLDSTEIN, MD:* Recognition of the association between exposure to ozone or NO_2 and the development of respiratory infection has resulted in the use of animal models of infection to evaluate this pathophysiologic relationship.[49,50] As a surrogate for the process in humans, animal models that show the physiologic interaction between bacteria and host antibacterial defense systems have a number of virtues that provide bases for extrapolation. Animal and human antibacterial defenses consist of an aerodynamic filtration system, transport mechanisms for removing bacteria, phagocytes (alveolar macrophages and, when required, polymorphonuclear leukocytes) and immune secretions of lymphocytes and plasma cells. In rodents and humans, these components act in concert to maintain the lung free of bacteria.[49-52]

The aerosol model in which rodents inhale bacteria and in which measurements are made of rates of physical removal and intrinsic bacterial killing permits testing of the aforementioned components as well as the entire antibacterial system.[49,50] When this rodent model is used, the animals are exposed for variable periods to different concentrations of photochemical oxidants, and decreases in antibacterial activity reflect quantitative impairments in function. Because of the similarities of human and rodent defense systems, impairments observed in rodents presumably occur in humans, and although quantitative dose-response extrapolations cannot be made from the rodent data, qualitative conclusions are justified. That is, the identification of a pollutant-induced defect, such as an inability of alveolar macrophages to kill inhaled bacteria or a delay in mucociliary clearance, indicates that the abnormality may be expected in human exposures.

When mice are infected with *Staphylococcus aureus* and then exposed for five hours to increasing concentrations of ozone beginning at 0.62 ppm, the ability of the alveolar macrophage to eradicate the invading microbe is progressively impaired.[53] This abnormality is due primarily to diminished intercellular killing of ingested microorganisms and secondarily to reduced rates of ingestion.[54] As a result of these abnormalities, staphylococci that normally do not replicate within alveolar macrophages proliferate, destroying the phagocyte (Figure 3).[54,55] When the same animal model is used to study NO_2, progressive impairments in bacterial killing are first noted after a four-hour exposure to 7.0 ppm of NO_2, showing the lesser toxicity of this pollutant compared with ozone.[56] More prolonged exposures to NO_2 produce impairments in bacterial killing at lower concentrations (2.0 ppm), confirming the cumulative toxicity of NO_2.[56] At threshold concentrations for inducing abnormalities in phago cytic function, neither ozone nor NO_2 causes serious impairment in mucociliary clearance rates.[53,57,58] Thus, both ozone and NO_2 can inhibit the capacity of alveolar macrophages to maintain pulmonary sterility, thereby rendering the lung vulnerable to bacterial infection; moreover, consistent with previous conclusions, at nearly ambient levels short-term exposure to ozone is much more toxic than is short-term exposure to NO_2.

Coffin and Blommer,[59] Ehrlich,[60,61] Gardner[51] and Gardner and Graham[62] have extended these pathophysiologic observations by developing a rodent model, often referred to as the "infectivity model," linking interference with antibacterial activity to mortality. Instead of infecting rodents with minimally virulent staphylococci, these investigators expose

*Chief, Division of Infectious and Immunologic Diseases, Department of Internal Medicine, University of California, Davis, School of Medicine.

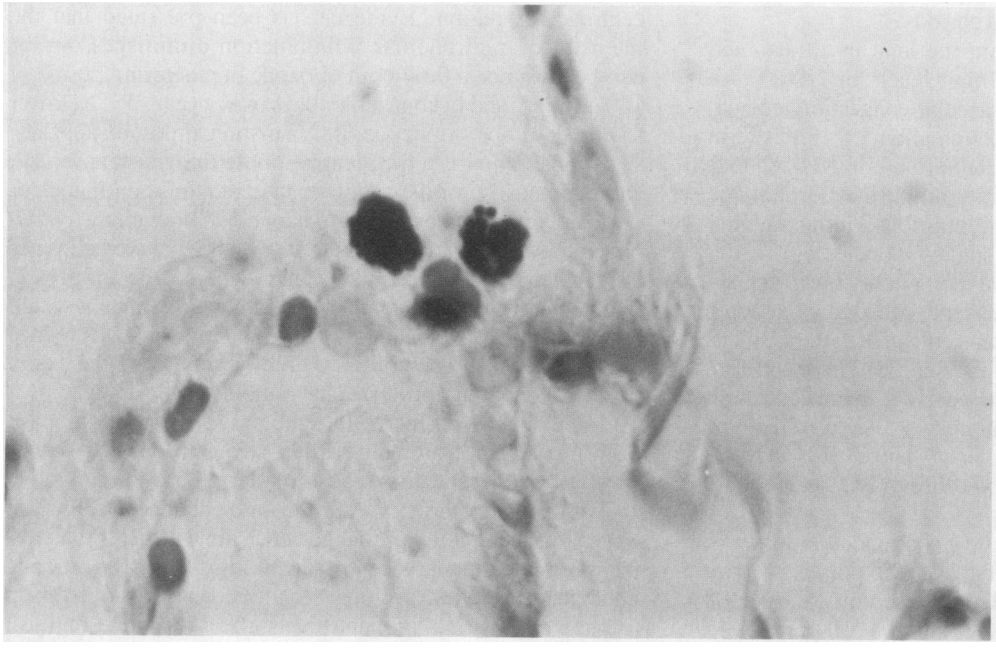

Figure 3.—Two large clumps of staphylococci that appear to be growing out from unidentified cells of the pulmonary alveolar region. The specimen is from a rat exposed to 2.5 ppm of ozone for four hours. (Brown-Brenn stain, reduced from magnification × 2,200.) (Reproduced with permission from Goldstein et al.[54])

the animals to highly virulent group C streptococci[59,62] or *Klebsiella* species[60,61] before or following pollutant exposure. When these pathogens are used, the pathophysiologic alterations in antibacterial defenses induced by the pollutant result in bacterial proliferation and excessive mortality. These investigations have shown that two-hour exposures to ozone concentrations as low as 0.1 ppm increase murine mortality from group C streptococcal infections[59] and that exposure to NO_2 concentrations as low as 3.5 ppm increases murine mortality from klebsiellal infections.[61] The infectivity model has also been used to show that one- to two-hour exposures to much higher concentrations (5 to 25 ppm and 50 ppm) of NO_2 are required to kill infected hamsters and squirrel monkeys, emphasizing the differences in susceptibility to pollutant toxicity among species.[63] Thus, results with aerosol models of infection show that short-term exposures to ambient levels of ozone but not NO_2 impair normal pulmonary antibacterial defenses by interfering with the capacity of alveolar macrophages to kill inhaled bacteria and are associated with increased mortality. Furthermore, insofar as these results can be applied to humans, they suggest that short-term exposures to ambient levels of ozone may adversely affect the function of human alveolar macrophages.

Long-term Effects of NO_2

The few studies in which the effect of prolonged exposure to ozone or NO_2 on murine capacity to survive aerosol challenges with virulent group C streptococci or *Klebsiella pneumoniae* has been assessed have shown pollutant-induced increases in mortality similar to those observed in short-term studies.[64,65] Mice exposed to peak daily doses of 0.2 ppm of ozone or 0.94 ppm of NO_2 for three hours per day have increased mortality when challenged with group C streptococci following six but not three months of exposure.[64] The threshold level for NO_2-induced mortality in the infectivity model is in the range of 0.38 ppm of NO_2, which did not produce increased mortality following nine months of continuous exposure (group C streptococci),[64] and 0.50 ppm, which caused increased mortality after three months of continuous exposure *(K pneumoniae)*.[65] When exposures are to both pollutants, an additive effect is sometimes observed.[64,66,67] Viewed in relationship to ambient concentrations of ozone and NO_2, these results are in accord with previous findings that ambient levels of ozone but not NO_2 impair pulmonary systems.

In the above studies healthy animals were used that were infected before or following the pollutant exposure. Because humans with underlying pulmonary infections may be especially vulnerable to oxidant-induced injury, animal models with chronic infections are needed to assess the role of photochemical oxidants as an aggravating insult.[68,69]

We recently tested the effect of a four-week exposure to 0.64 ppm of ozone in one such model in which a smoldering *Pseudomonas* infection was produced by intratracheally instilling *Pseudomonas*-containing agar beads.[70] Although the pollutant caused anatomic damage, the infection itself was unaffected, indicating that the pollutant does not inhibit antibacterial defenses when infecting bacteria are confined within granulomas. Future studies with animal models mimicking nongranulomatous bronchial infections, such as those produced by *Legionella pneumophila,* are needed to further define the effect of long-term exposures to ambient levels of photochemical oxidants on a chronically infected lung.

In addition to potentiating infection, photochemical oxidants may act as mutagens.[71-74] Chromosomal changes have been reported in circulating lymphocytes of Chinese hamsters following five-hour exposures to 0.2 ppm of ozone[73] and in lymphocytes from humans exposed for six to ten hours to 0.5 ppm of ozone.[74] However, in other studies carried out in nearly identical fashion in mice and humans, cytogenetic damage was not detected.[75,76] Because of these conflicting results, the mutagenic potential of ozone for animal cells is unproved. When compared with known mutagens like ultraviolet light and x-rays in eukaryotic systems, ozone acts as a weak mutagen, suggesting that the genetic risk, if it occurs, is small.[77]

NO_2, by virtue of its capacity to form nitrites, can convert secondary amines to carcinogenic nitrosamines.[78] Iqbal and co-workers reported that microgram amounts of *N*-nitrosomorpholine were produced in mice gavaged with morpholine and then exposed to 0.2 to 50 ppm of NO_2 for four hours.[79] These results were confirmed by van Stee and colleagues,[80] who have also shown a marginally significant increase in the incidence of pulmonary adenomas in CD-1 mice exposed to 1 to 2 ppm of NO_2 for 6 hours daily, 5 days per week for 30 weeks while ingesting morpholine from drinking water.[81] Because of the artificial conditions of these experiments and because malignant tumors have not been observed in mice or hamsters exposed to 4.0 ppm of NO_2 for as long as 16 months, the biologic significance of these controversial studies is uncertain.[82,83] This is an active area of research in which future studies should result in more definitive conclusions of the carcinogenic potential of nitrogen dioxide.

In summary, studies of the effect of short-term exposure to ambient concentrations of ozone in rodent models of infection show that the pollutant inhibits the capacity of alveolar macrophages to kill intrapulmonary bacteria and that virulent bacteria proliferate and kill the host as a result of this abnormality. Whether these adverse effects occur in humans is unknown, but because infection is a conceivable consequence of exposure to ambient concentrations of ozone, this adverse effect is of potential importance. NO_2 also inhibits the ability of alveolar macrophages to kill inhaled bacteria. This pollutant, however, is less toxic than ozone, requiring exposure conditions much above ambient levels. Studies of the mutagenic and carcinogenic potential of these pollutants show that ozone is a weak mutagen in eukaryotes and that its mutagenicity for human cells is uncertain. NO_2, in experimental situations differing significantly from environmental conditions, reacts with secondary amines to form potentially carcinogenic nitrosamines. The significance of these observations for human exposure is unknown.

Cost-Benefit Estimates for Controlling Photochemical Oxidant Pollution

PAOLO F. RICCI, PHD:* Because photochemical oxidant pollution is a humanmade problem, it is readily controlled by reducing emissions from mobile and stationary sources. This salient fact is the basis for the Clean Air Act requirement that primary national ambient air-quality standards be determined

*Project Manager, Electric Power Research Institute, Palo Alto, California, and Adjunct Professor of Environmental Management, University of San Francisco.

solely as a function of health risk. (In analyzing the National Ambient Air Quality Standards provision, the Supreme Court held that "claims of economic or technological infeasibility may not be considered by the Administrator in evaluating a state requirement that primary ambient air quality standards be met in the mandatory three years."[84]) To accomplish this objective, the Environmental Protection Agency (EPA) established standards for photochemical oxidant and nitrogen dioxide on health-risk assessments alone and then promulgated regulations to achieve these standards. Specifically, NO_2 emissions that averaged more than 3 grams per mile in gasoline-powered automobiles in the 1970s were limited to 2 grams per mile in 1980 models and to less than 1 gram per mile in present models.[85] Allowable NO_2 emissions from fossil-fuel power plants, which had increased from 5.8 to 6.8 million metric tons per year from 1970 to 1978,[86] were set in the most recent source-performance standards at 0.5 to 0.8 lb per million British thermal units, depending on the type of coal.[87] Because these regulations were designed to maximize protection, they were costly but consistent with the intent of the mandate of the Clean Air Act.

However, as we have become aware of the finite nature of our resources, the policy of eradicating risk to the greatest extent possible has been declining in popularity, and considerations of societal benefit versus societal cost have replaced demands for a technologically risk-free society.[88] Accordingly, in decisions involving environmental control, the benefits of control strategies are now weighed against the economic impact on transportation and energy industries. In the following discussion I will review economic information on the cost-benefit balances involved in these photochemical oxidant and NO_2 issues.

In recent years, the cost of reducing nitrogen dioxide emissions of mobile and stationary power plant sources has been assessed economically.[89,90] According to figures released by the EPA, the annual cost for mobile-source pollution control was slightly less than $6 billion in 1977 and represented 0.25% of the 1977 gross national product.[89] In future years, if the strictest standards of the Clean Air Act—particularly the NO_x standard of 0.4 gram per mile—are enforced, the annual cost will reach $11 billion.[90] As an example of individual costs, automobile purchasers paid an extra $480 for emission control equipment to achieve the nitrogen dioxide standard of 1.0 gram per mile on 1981 models.[85] Additional annual expenses were incurred in lessened fuel economy, which in 1977, when gasoline was $0.35 a gallon, averaged $13.70, and maintenance, which for the same year averaged $7.50.[91] These costs allow a 94% reduction in emissions from the 1960 level and, as is shown in Figure 4, further reductions in nitrogen dioxide emissions will be even more expensive, owing to the exponential increase in cost.

The investment cost to the fuels and energy industry in reducing air pollution is estimated at $3 billion per year for the period 1977 to 1981. The removal of sulfur oxides and particulates with nitrogen dioxide accounts for approximately $300 million of the annual estimate. The $300 million represents $5 to $10 per kW of installed capacity, which is less than 1% of the total cost of the electricity generated.[92] These costs apply for the least expensive, low NO_2 burner, abatement technologies. More expensive technologies, like flue gas denitrification, have a capital cost of $35 to $45 per kW installed capacity, which is 4% to 8% of the total cost of the generated electricity.[92] Newer methods such as the Hitachi-Zosen system, which uses a postcombustion process to achieve a 90% efficiency in removing NO_2, are even more costly, ranging from $65 to $95 per kW installed capacity.[93] Thus, if further reductions in stationary-source emissions of NO_2 are demanded, in the absence of improved technology, the expense is likely to increase considerably.

As is apparent from the previous discussions of the health effects of photochemical oxidants, the benefits obtained by

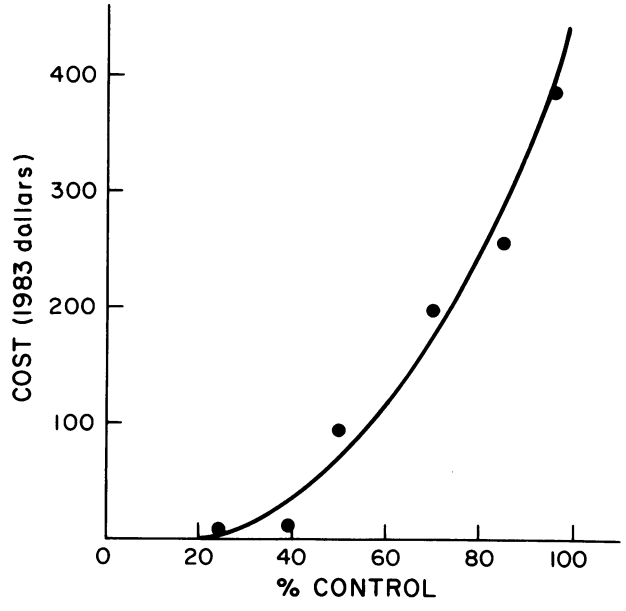

Figure 4.—Cost-control relationship for nitrogen dioxide. (Modified from Schwing et al[91] by the gross national product price deflator [1970 = 91.4; 1983 = 213.4, first quarter].)

reducing NO_2 emissions are fraught with uncertainty. Most analysts have assumed that mortality and morbidity are consequences of exposure to ambient levels of photochemical oxidants.[90,91] When these assumptions are used, the benefits of total abatement of NO_2 pollution vary between $183 million and $1.6 billion for mobile-source emissions in some studies to as much as $1.5 to $5 billion in other studies, which included material damage.[94] Assessing stationary-source benefits from eliminating NO_2 emissions is even more uncertain because of the role of other pollutants like sulfur dioxide, particulates and carbon monoxide.[95] Benefits from preventing agricultural losses due primarily to ozone are estimated to be $100 million per year in the south coast air basin of California, an area with high photochemical pollution and high agricultural production.[96] Nationwide benefits are estimated to be $278 million (EPA, unpublished data, cited by Leung and co-workers[96]).

Although considerable uncertainty exists in determining the cost-benefit relationships, some experts consider the costs in controlling photochemical oxidants to exceed the benefits.[90,91,97] The annual costs computed by these economists for controlling mobile-source emissions are upwards of $5 billion per year, an amount in excess of their estimates of benefit. However, intangible nonmarket benefits such as diminished sensory discomfort and annoyance and increased pleasure from the enjoyment of a cleaner environment are not included in these estimates.[91] Much of the public is willing to pay for these intangible benefits, and in recent years this number has increased, so that those nonmarket benefits are assuming increased importance.

Summary

ELLIOT GOLDSTEIN, MD: Several conclusions can be drawn from the preceding presentations. First, results from volunteer studies, epidemiologic investigations and animal experiments show similarities in threshold for ozone-induced photochemical oxidant effects. Short-term exposures to levels of 0.3 ppm or greater are clearly detrimental to health, causing respiratory symptoms and diminished ventilatory function. Exposure to lower levels (0.12 to 0.3 ppm), which occur often in heavily polluted areas like the Los Angeles basin, are associated with a higher prevalence of respiratory symptoms, impairment in exercise tolerance and possible increases in incidence of asthmatic attacks and reductions in ventilatory function. Although animal models suggest that these levels enhance susceptibility to infection, no data from studies in humans support such an occurrence. Exposure to lower concentrations of ozone does not cause disease, dysfunction or discomfort, even in hypervulnerable populations. Thus, the present standard of 0.12 ppm of oxidant for a one-hour period is at or beneath the probable-effects level for photochemical oxidant injury. The margin of safety, however, is small, and future studies may show that some persons are vulnerable to injury from 0.12 ppm of ozone.

Second, the available information indicates that discomfort and impairment during athletic activities are the likeliest consequences of short-term exposure to oxidant concentrations at the present 0.12 ppm standard. Athletes in competitions requiring strenuous activity, such as bicycle riding or distance running, may not do as well when photochemical oxidant levels reach 0.12 ppm. Because we are a sports-minded country, a deleterious effect of this kind has enormous social importance.

Third, because of the paucity of epidemiologic data correlating prolonged exposure to photochemical oxidants with disease, dysfunction and discomfort, the risk for populations living in heavily polluted areas is uncertain. Studies do not show an increase in disease incidence or enhancement of underlying pulmonary illnesses as a result of pollutant exposure. Small reductions in ventilatory function and increased incidence in self-limiting respiratory symptoms are possible consequences of such exposures, but definitive proof is lacking. This lack of effect from exposure to ambient levels of photochemical oxidants agrees with results from studies in animals showing only modest cellular defects following similar exposures. However, because of the importance of definitively determining the risk to humans from long-term exposure to photochemical oxidants, attaining conclusive epidemiologic data should be a major goal of health agencies. The magnitude of the health and economic considerations involved in establishing standards for photochemical oxidant exposures mandates that despite their difficulty, epidemiologic studies should be concluded within this decade to determine the risk.

Fourth, an abundant body of evidence from studies with volunteers, exposed populations and animal models indicates that short-term exposures to ambient levels of NO_2 do not cause disease in healthy persons or aggravate underlying pulmonary diseases. Short-term exposures to high ambient levels of NO_2 may provoke self-limiting symptoms reflecting respiratory illness or irritation in children, but this association is tenuous and inconclusive. Few reliable data exist for assessing the effect on humans of prolonged exposure to high ambient levels of nitrogen dioxide. Studies in children suggest that permanent injury is not a consequence of these exposures, and investigations with various animal models support the likelihood that present levels of NO_2 are innocuous insofar as the respiratory system is concerned. One potentially hazardous effect of NO_2 is the capacity of the pollutant to form carcinogenic nitrosamines in animals tested under highly artificial laboratory conditions. The significance of these observations awaits results from experiments done under realistic conditions. Thus, at present, no definitive evidence exists linking prolonged human exposure to ambient levels of NO_2 to disease, dysfunction or discomfort, and, on the basis of current knowledge, the annual standard of 0.05 ppm of NO_2 is much below the minimum-effects level.

Fifth, billions of dollars are spent annually to limit emissions of NO_2 from automobiles and industrial processes and to control photochemical oxidant pollution. As a result of these efforts, atmospheric levels of air pollution have not worsened and in some areas they have diminished.[98] This improvement in air quality has undoubtedly benefited residents of these areas. Whether these benefits, which primarily affect comfort and athletic ability, justify the present expense or warrant greater or lesser expense is a complex regulatory issue in which Solomon-like decisions are required to ensure the safety and well-being of the populace while at the same time allowing society to benefit from technology.

REFERENCES

1. Schwartz LW, Dungworth DL, Mustafa MC, et al: Pulmonary responses of rats to ambient levels of ozone—Effects of 7-day intermittent or continuous exposure. Lab Invest 1976 Jun;34:565-578

2. Plopper CG, Dungworth DL, Tyler WS, et al: Pulmonary alterations in rats

exposed to 0.2 and 0.1 ppm ozone: A correlated morphological and biochemical study. Arch Environ Health 1979 Nov-Dec; 34:390-395

3. Castleman WS, Tyler WS, Dungworth DL: Lesions in respiratory bronchioles and conducting airways of monkeys exposed to ambient levels of ozone. Exp Mol Pathol 1977; 26:384-400

4. Castleman WS, Dungworth DL, Schwartz LW, et al: An ultrastructural and autoradiographic study of epithelial cell injury and renewal in rhesus monkeys exposed to ozone. Am J Pathol 1980 Mar; 98:811-840

5. Coffin DL, Stokinger HE: Biological effects of air pollutants, *In* Stern AC (Ed): Air Pollution, Vol 2, 3rd Ed. London, Academic Press, 1977, pp 231-360

6. Jaffe LS: The biological effects of ozone on man and animals. Am Indust Hyg Assoc J 1967 May-Jun; 28:267-277

7. California Air Resources Board: California Air Quality Data, January-February-March 1978, Vol X. Sacramento, Calif, Technical Services Division, 1978, p 19

8. DeMore WB, Romanovsky JC, Feldstein M, et al: Interagency Comparison of Iodometric Methods for Ozone Determination: Calibration in Air Monitoring, ASTM STP 598. American Society for Testing and Materials, 1976, pp 131-143

9. Bruch JD, Schlipköter HW: Veränderungen der Lungenalveolen bei der Maus nach chronischer Exposition mit Ozon in niedriger Konzentration. Virchows Arch (Pathol Anat) 1973; 358:355-368

10. Castleman WS, Dungworth DL, Tyler WS: Cytochemically detected alterations of lung acid phosphatase reactivity following ozone exposure. Lab Invest 1973 Mar; 29:310-319

11. Freeman GR, Stephens RJ, Coffin DL, et al: Changes in dogs' lungs after long-term exposure to ozone—Light and electron microscopy. Arch Environ Health 1973 Mar; 26:209-216

12. Scheel LD, Dobrogorski OJ, Mountain JT, et al: Physiologic, biochemical, immunologic and pathologic changes following ozone exposure. J Appl Physiol 1959 Jan; 14:67-80

13. Stephens RJ, Sloan MF, Evans MJ, et al: Early response of lung to low levels of ozone. Am J Pathol 1974 Jan; 74:31-58

14. Mellick PW, Dungworth DL, Schwartz LW, et al: Short-term morphologic effects of high ambient levels of ozone on lungs of rhesus monkeys. Lab Invest 1977 Jan; 36:82-90

15. Castleman WL, Dungworth DL, Tyler WS: Intrapulmonary airway morphology in three species of monkeys: A correlated scanning and transmission electron microscopic study. Am J Anat 1975 Jan; 142:107-122

16. Miller FJ: Similarity between man and laboratory animals in regional pulmonary deposition of ozone. Environ Res 1978; 17:84-101

17. Evans MJ, Johnson LV, Stephens RJ, et al: Renewal of the terminal bronchiolar epithelium in the rat following exposure to NO_2 or O_3. Lab Invest 1976 Sep; 35:246-257

18. Evans MJ, Johnson LV, Stephens J, et al: Cell renewal in the lungs of rats exposed to low levels of ozone. Exp Mol Pathol 1976; 24:70-83

19. Lum H, Schwartz LW, Dungworth DL, et al: A comparative study of cell renewal after exposure to ozone or oxygen—Response of terminal bronchiolar epithelium in the rat. Am Rev Respir Dis 1978 Aug; 118:335-345

20. Stokinger HE, Wagner WD, Dobrogorski OJ: Ozone toxicity studies—III. Chronic injury to lungs of animals following exposure to low level. Arch Ind Health 1957; 16:514-522

21. Gross P, Scheel LD, Stokinger HE: Ozone toxicity studies; destruction of alveolar septa—a precursor of emphysema? Medicina Thoracalis 1965; 22:376-381

22. Boorman GA, Schwartz LW, Dungworth DL: Pulmonary effects of prolonged ozone insult in rats—Morphometric evaluation of the central acinus. Lab Invest 1980 Feb; 43:108-115

23. Moore PF, Schwartz LW: Morphologic effects of prolonged exposure to ozone and sulfuric acid aerosol on the rat lung. Exp Mol Pathol 1981; 35:108-123

24. Eustis SL, Schwartz LW, Kosch PC, et al: Chronic bronchiolitis in nonhuman primates after prolonged ozone exposure. Am J Pathol 1981 Nov; 105:121-137

25. Fujinaka LE, Hyde DM, Plopper CG, et al: Response of bronchiolar epithelium and peribronchiolar connective tissue to chronic ozone exposure (Abstr). Am Rev Respir Dis 1983; 127:165

26. Wagner CD, Jackson AC, Berry JD, et al: The effects of long-term, low-level ozone exposure to static, dynamic and oscillatory pulmonary mechanics in monkeys (Abstr). Am Rev Respir Dis 1982; 125:147

27. Hine CM, Meyers FN, Wright RW: Pulmonary changes in animals exposed to nitrogen dioxide, effects of acute exposures. Toxicol Appl Pharmacol 1970 Jan; 16:201-213

28. Steadman BL, Jones RA, Rector DE, et al: Effects on experimental animals of long-term continuous inhalation of nitrogen dioxide. Toxicol Appl Pharmacol 1966 Jul; 9:160-170

29. Carson TR, Rosenholtz MS, Wilinski FT, et al: The responses of animals inhaling nitrogen dioxide for single, short term exposures. Am Ind Hyg Assoc J 1962 Nov-Dec; 23:457-462

30. Henry MC, Ehrlich R, Blair WH: Effect of nitrogen dioxide on resistance of squirrel monkeys to Klebsiella pneumoniae infection. Arch Environ Health 1969 Mar; 18:58-87

31. Dowell AR, Kilburn KK, Pratt PC: Short-term exposure to nitrogen dioxide—Effects on pulmonary ultrastructure, compliance, and the surfactant system. Arch Intern Med 1971 Jul; 128:74-80

32. Stephens RJ, Freeman G, Evans MJ: Early response of lungs to low levels of nitrogen dioxide—Light and electron microscopy. Arch Environ Health 1972 Mar; 24:160-179

33. Keller MD, Lanese RR, Mitchell RI, et al: Respiratory illness in households using gas and electricity for cooking—I. Survey of incidence. Environ Res 1979 Aug; 19:495-503

34. Freeman G, Jukos LT, Furiosi NJ, et al: Pathology of pulmonary disease from exposure to interdependent ambient gases (nitrogen dioxide and ozone). Arch Environ Health 1974 Oct; 29:203-210

35. Mustafa MG, Lee SD: Biological effects of environmental pollutants: Methods for assessing biochemical changes, *In* Lee SD, Mudd JB (Eds): Toxic Effect of Environmental Pollutants. Ann Arbor, Mich, Ann Arbor Science, 1979, pp 165-178

36. Ehrlich R, Henry MC: Chronic toxicity of nitrogen dioxide—I. Effect of resistance to bacterial pneumonia. Arch Environ Health 1968 Dec; 17:860-865

37. Freeman G, Furiosi NJ, Haydon GB: Effects of continuous exposure to 0.8 ppm NO_2 on respiration of rats. Arch Environ Health 1966 Oct; 13:454-456

38. Freeman G, Stephens RJ, Crane SC, et al: Lesion of the lung in rats continuously exposed to 2 ppm of nitrogen dioxide. Arch Environ Health 1968 Aug; 17:181-182

39. Wagner WD, Duncan BR, Wright PG, et al: Experimental study of threshold limit of NO_2. Arch Environ Health 1965 Mar; 10:455-456

40. Fenters JD, Findley JC, Port CD, et al: Chronic exposure to nitrogen dioxide—Immunologic, physiologic and pathologic effects in virus-challenged squirrel monkeys. Arch Environ Health 1973 Aug; 27:85-89

41. Freeman G, Crane SC, Stephens RJ, et al: The subacute nitrogen dioxide-induced lesion of the rat lung. Arch Environ Health 1969 Apr; 18:609-612

42. Nakajima T, Hattori S, Tateisni R, et al: Morphological changes in the bronchiole alveolar system of mice following continuous exposure to low concentrations of nitrogen dioxide and carbon monoxide. J Jpn Soc Chest Dis 1972; 10:16-22 (Japanese)

43. Furiosi NJ, Crane SC, Freeman G: Mixed sodium chloride aerosol and nitrogen dioxide in air—Biologic effects on monkeys and rats. Arch Environ Health 1973 Dec; 27:405-408

44. Hyde D, Orthoefer J, Dungworth D, et al: Morphometric and morphologic evaluation of pulmonary lesions in beagle dogs chronically exposed to high ambient levels of air pollutants. Lab Invest 1978 Apr; 38:455-469

45. Freeman GS, Crane SC, Stephens RJ, et al: Environmental factors in emphysema and a model system with NO_2. Yale J Biol Med 1968 Jun; 40:566-575

46. Haydon GB, Davidson JT, Lillington GA, et al: Nitrogen dioxide-induced emphysema in rabbits. Am Rev Respir Dis 1967 May; 95:797-805

47. Port CD, Ketels KV, Coffin DL, et al: A comparative study of experimental and spontaneous emphysema. J Toxicol Environ Health 1977 Jan; 2:589-604

48. Plopper CG, Chow CK, Dungworth DL, et al: Effect of low level of ozone on rat lungs—II. Morphological responses during recovery and reexposure. Exp Mol Pathol 1978; 29:400-411

49. Goldstein E, Jordan GW, MacKenzie MR, et al: Methods for evaluating the toxicological effects of gaseous and particulate contaminants on the pulmonary microbial defense system. Annu Rev Pharmacol Toxicol 1976; 16:447-463

50. Jakab GJ: Nitrogen dioxide-induced susceptibility to acute respiratory illness—A perspective. Bull NY Acad Med 1980 Nov-Dec; 56:847-855

51. Gardner DE: Use of experimental airborne infections for monitoring altered host defenses. Environ Health Perspect 1982 Feb; 43:99-107

52. Green GM, Jakab GJ, Low RB, et al: State of the art—Defense mechanisms of the respiratory membrane. Am Rev Respir Dis 1977 Mar; 115:479-514

53. Goldstein E, Tyler WS, Hoeprich PD, et al: Adverse influence of ozone on pulmonary bactericidal activity of murine lung. Nature 1971 Jan 22; 229:262-263

54. Goldstein E, Lippert W, Warshauer D: Pulmonary alveolar macrophage: Defender against bacterial infection of the lungs. J Clin Invest 1974 Sep; 54:519-528

55. Kimura A, Goldstein E: Effect of ozone on concentrations of lysozyme in phagocytizing alveolar macrophages. J Infect Dis 1981 Feb; 143:247-251

56. Goldstein E, Eagle MC, Hoeprich PD: Effect of nitrogen dioxide on pulmonary bacterial defense mechanisms. Arch Environ Health 1973 Apr; 26:202-204

57. Kenoyer JL, Phalen RF, Davis JR: Particle clearance from the respiratory tract as a test of toxicity: Effect of ozone on short and long term clearance. Exp Lung Res 1981; 2:111-118

58. Giordano AM, Morrow PE: Chronic low-level nitrogen dioxide exposure and mucociliary clearance. Arch Environ Health 1972 Dec; 25:443-449

59. Coffin DL, Blommer EJ: The influence of cold on mortality from streptococci following ozone exposure. J Air Pollut Control Assoc 1965; 15:523-524

60. Ehrlich R: Effect of air pollutants on respiratory infection. Arch Environ Health 1963 May; 6:638-642

61. Ehrlich R: Effect of nitrogen dioxide on resistance to respiratory infection. Bacteriol Rev 1966 Mar; 30:604-614

62. Gardner DE, Graham JA: Increased pulmonary disease mediated through altered bacterial defenses in pulmonary macrophages and epithelial cells, *In* Sanders CL, Schneider RP, Dagel GE, et al (Eds): Proceedings of the 16th Annual Hartford Biology Symposium, Richland. Oak Ridge, Tenn, Dept of Energy Technical Information Center, Energy Research and Development Administration, 1972, pp 1-21

63. Ehrlich R: Interaction between environmental pollutants and respiratory infections. Environ Health Perspect 1980 Feb; 35:89-100

64. Ehrlich R: Changes in susceptibility to respiratory infection caused by exposures to photochemical oxidant pollutants, *In* Lee SD, Mustafa MG, Mehlman MA (Eds): Advances in Modern Environmental Toxicology—Vol 5, The Biomedical Effects of Ozone and Related Photochemical Oxidants. Princeton, NJ, Princeton Scientific Publishers, 1983, pp 273-285

65. Ehrlich R, Henry MC: Chronic toxicity of nitrogen dioxide—I. Effect of resistance to bacterial pneumonia. Arch Environ Health 1968 Dec: 17:860-865

66. Goldstein E, Warshauer D, Lippert W, et al: Ozone and nitrogen dioxide exposure. Arch Environ Health 1974 Feb; 28:85-90

67. Ehrlich R, Findley SC, Fenters JD, et al: Health effects of short-term inhalation of nitrogen dioxide and ozone mixtures. Environ Res 1977 Oct; 14:223-231

68. Cash HA, Woods DE, McCullough B, et al: A rat model of chronic respiratory infection with *Pseudomonas aeruginosa*. Am Rev Respir Dis 1979 Mar; 119:453-459

69. Davis GS, Washington CW Jr, Gump DW, et al: Legionnaires' pneumonia after aerosol exposure in guinea pigs and rats. Am Rev Respir Dis 1982 Dec: 126:1050-1057

70. Sherwood RL, Kimura A, Donovan RM, et al: Effect of 0.64 ppm ozone on rats with chronic pulmonary bacterial infection. J Toxicol Environ Health 1984 May-Jun; 13:893-904

71. Brinkman R, Lamberts HB, Veningu TS: Radiomimetic toxicity of ozonized air. Lancet 1964 Jan 18; 1:133-136

72. Von Nieding G: Possible mutagenic properties and carcinogenic action of the irritant gaseous pollutants NO_2,SO_2. Exp Health Perspect 1978 Feb; 22:91-92

73. Zelac RE, Cromroy HL, Bolch WE Jr, et al: Inhaled ozone as a mutagen—II. Effect on the frequency of chromosome aberrations observed in irradiated Chinese hamsters. Environ Res 1971 Oct; 4:325-342

74. Merz T, Bender MA, Kerr HD, et al: Observations of aberrations in chromosomes of lymphocytes from human subjects exposed to ozone at a concentration of 0.5 ppm for 6 and 10 hours. Mutat Res 1975; 31:299-302

75. Gooch PC, Creasia DA, Brewen JG: The cytogenetic effects of ozone: Inhalation and *in vitro* exposures. Environ Res 1976 Oct; 12:188-195

76. McKenzie WH, Knelson JH, Rummo NJ, et al: Cytogenetic effects of inhaled ozone in man. Mutat Res 1977; 48:95-102

77. Dubeau H, Chung YS: Genetic effects of ozone—Induction of point mutation and genetic recombination in *Saccharomyces cerevisiae*. Mutat Res 1982; 102:249-259

78. Mirvish SS: Formation of N-nitroso compound: Chemistry, kinetics and *in vivo* occurrence. Toxicol Appl Pharmacol 1975 Jun; 31:325-351

79. Iqbal ZM, Dahl K, Epstein SS: Role of nitrogen dioxide in the biosynthesis of nitrosamines in mice. Science 1980 Mar; 207:1425-1477

80. Van Stee EW, Sloane RA, Simmons JE, et al: Formation of *N*-nitrosomorpholine in CD-1 Mice exposed by inhalation to nitrogen dioxide and by gavage to morpholine. JNCI 1983 Feb; 70-375-379

81. Van Stee EW, Boorman GA, Haseman JK: Pulmonary adenomas in mice exposed to NO_2 by inhalation and morpholine by ingestion (Abstr). Pharmacologist 1980; 22:158

82. Henschler D, Ross W: Zur Frage einer cancerogenen Wirkung inhalierter Stickstoffoxyde. Naunyn Schmiedeberg Arch Exp Pathol 1966; 253:495-507

83. Ross W, Henschler D: Fehlen einer cancerogenen Wirkung von nitrosen Gasen beim Goldhamster. Experientia 1968; 24:55-57

84. Union Electric Company v Environmental Protection Agency, 427 US26, 265, 1976

85. The Clean Air Act—Nitrogen Dioxides. Recommendations for Improving Mobile Source Provisions of the Clean Air Act. General Motors Corporation, January, 1982 (Pamphlet)

86. National Air Pollutant Emission Estimates, 1970-1981, Environmental Protection Agency publication No. EPA-450/4-82-012. Government Printing Office, 1982, pp 1-35

87. Environmental Protection Agency. New Stationary Sources Performance Standards; Electric Utility Steam Generating Units. Final Rule pp 33580-33624, FR 33580 Action Final Rule 40 CFR, P60, 1979

88. Ricci PF, Molton LS: Risk and benefit in environmental law. Science 1981 Dec 4; 214:1096-1100

89. Report to Congress: The Cost of Clean Air and Water, Environmental Protection Agency publication No. EPA-230/3-79-001. Office of Planning and Management, 1979 Aug, pp X-XIX

90. Lave LB, Seskin EP: Air pollution and human health, chap 10, The Benefits and Costs of Air Pollution Abatement. Baltimore, Johns Hopkins University Press, 1977, pp 209-234

91. Schwing RC, Southworth BW, von Buseck CR, et al: Benefit-cost analysis of automotive emission reduction. J Environ Econ Manage 1980; 7:44-64

92. Torrens IM: Cleaning up coal pollution: Costs and benefits. OECD [Organization for Economic Cooperation and Development] Observer 1982; 118:22-27

93. Damon JE, Scheck RW, Cicchanowiez JE: Economics of SCR Postcombustion NO_2 Control Processes. Presented at a Joint Symposium on Stationary Combustion NO Control Processes, November 1-4, 1982, Dallas, Texas

94. Report by the Coordinating Committee on Air Quality Studies: National Academy of Sciences Air Quality and Automobile Emission Control, Vol 4—The Costs and Benefits of Automobile Emission Control, National Academy of Sciences, National Academy of Engineering serial No. 93-24. Government Printing Office, 1974, p 412

95. Mendelsohn R: An economic analysis of air pollution from coal-fired power plants. J Environ Econ Manage 1980; 7:30-43

96. Leung SK, Reed W, Geng S: 1982 estimates of ozone damage to selected crops grown in Southern California. J Air Pollut Control Assoc; 32:160-164

97. Innes WB: Effect of Nitric Oxide Emissions on Photochemical Smog. Upland, Calif, Purad Inc Publication, 1978, pp 116-124

98. Guidotti TL: The higher oxides of nitrogen: Inhalation toxicology. Environ Res 1978 Jun; 15:443-472